REMARKS

This Amendment is in response to the Final Office Action dated August 17, 2004. In the Office Action, Claims 1-3 and 5-6 are rejected under 35 U.S.C. §112, first and second paragraphs, and Claims 1-3 and 5-6 are rejected under 35 U.S.C. §103. Claims 1 and 3 have been amended, and Claims 5 and 6 have been cancelled without prejudice or disclaimer. Applicants believe that the rejections have been overcome in view of the amendments and for the reasons set forth below.

In the Office Action, Claims 1, 3, 5 and 6 are rejected under 35 U.S.C. §112, first paragraph, for containing subject matter allegedly not described in the specification. Claims 1, 3, 5 and 6 are also rejected under 35 U.S.C. §112, second paragraph, for indefiniteness. In response, Claims 1 and 3 have been amended. Accordingly, Claim 1 is now directed to a method for protecting *Lactobacillus johnsonii* La1 against stress, which includes the step of treating said *Lactobacillus johnsonii* La1 with about 3.5% NaCl for at least 15 minutes. Claim 3 is now directed to a method for protecting *Lactobacillus johnsonii* La1 against stress, which includes the step of exposing said *Lactobacillus johnsonii* La1 to a temperature of about 48°C for at least 15 minutes. Therefore, Applicants believe that the §112 rejections have been overcome and, thus, should be withdrawn.

In the Office Action, claims 1, 5 and 6 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,962,062 to Carrie et al.("*Carrie*"), in view of the APPLIED MICROBIOLOGY article to Broadbent ("*Broadbent*"), JOURNAL OF GENERAL MICROBIOLOGY article to Völker et al. ("*Völker*") and the APPLIED AND ENVIRONMENTAL MICROBIOLOGY article to Kilstrup et al. ("*Kilstrup*"). The Patent Office primarily relies on *Carrie* and, thus, relies on the combined and alleged teachings of the remaining references to remedy the deficiencies of *Carrie*. Applicants respectfully submit that the there is no motivation to combine the references with *Carrie*, and that the cited art, even if combinable, is deficient with respect to the claimed invention. Therefore, Applicants believe that this rejection is improper.

As discussed above, the present invention relates to a method of handling *Lactobacillus johnsonii* La1. More specifically, the claimed invention includes methods for protecting *Lactobacillus johnsonii* La1 against stress by making them more resistant to stresses of temperature and/or salt encountered in the environment.

Carrie fails to teach or suggest protecting *Lactobacillus johnsonii* La1. *Carrie* discloses dietetically balanced milk products, having a specific lipid profile. *Carrie* mentions *Lactobacillus johnsonii* La1 in the context of inoculating a mixture to begin the fermentation process in the production of a fermented and gelled milk product described in Examples 10-11. *See Carrie*, column 6, line 55 to column 7, line 19. The mixture undergoes pasteurization at 92°C and cools to a temperature of 43°C before 5% *Lactobacillus johnsonii* (La1, CNCM I-1227) is added as a fermentation starter culture. The mixture continues to cool to a temperature of 38°C to carry out fermentation. There is no teaching or suggestion in *Carrie* to maintain the temperature at 43°C for a period of time sufficient to allow adaptive processes leading to an adaptation to the higher temperature to occur to induce protection. As acknowledged by the Patent Office at page 3 of the Office Action, there is no teaching or suggestion in *Carrie* to expose the *Lactobacillus johnsonii* La1 to a temperature of about 48°C for at least 15 minutes as in the claimed invention. Therefore, *Carrie* fails to teach or suggest protecting *Lactobacillus johnsonii* La1.

Furthermore, *Carrie* fails to recognize the problem of bacterial protection against stress that Applicants have sought to overcome. *Carrie*, in fact, neither discloses a method of protecting *Lactobacillus johnsonii* La1 nor a need to protect *Lactobacillus johnsonii* La1. The fermentation method described in *Carrie* does not pretreat or challenge *Lactobacillus johnsonii* La1 with a stress to develop properties directed to withstand normally lethal conditions or become more resistant to the environment. At most, the skilled person has been taught by *Carrie* to add a starter culture of *Lactobacillus johnsonii* La1 in a specific volume to a fermentation culture at the elevated temperature (43°C) to cool down the whole fermentation culture to the desired fermentation temperature (38°C). Therefore, *Carrie* is not reasonably pertinent to the particular problem with which the present invention is concerned and is irrelevant. Based on at least these reasons, *Carrie*, on its own, is clearly distinguishable from the claimed invention and does not render obvious the present invention.

The Patent Office combines references that identify proteins synthesized by bacteria other than *Lactobacillus johnsonii* (La1) in response to stress conditions. Applicants respectfully submit that there is no motivation to combine *Carrie* with references that fail to even mention *Lactobacillus johnsonii* La1.

To support its combination and/or modification of the cited art to arrive at the claimed invention, Applicants respectfully submit that the Patent Office has applied hindsight reconstruction by selectively piecing together teachings of *Carrie* which happen to mention *Lactobacillus johnsonii* La1 in the context of fermentation of a milk product with the teachings of references that mention temperatureas and or salt concentrations in the context of strains of bacteria other than *Lactobacillus johnsonii* La1 in an attempt to re-create what the claimed invention discloses. Again, *Carrie* does not even suggest a problem or a need to protect *Lactobacillus johnsonii* La1. Why then would one skilled in the art be so inclined to apply to *Carrie* the alleged teachings regarding, for example, heat treatment in other bacteria as disclosed in *Broadbent*, *Völker* or *Kilstrup*? Applicants believe that, indeed, there is no motivation in the knowledge of the art or the references themselves to combine *Broadbent*, *Völker* or *Kilstrup* with *Carrie*. Without the requisite motivation to combine these teachings, their combination is clearly improper as being "hindsight reconstructive". *See In re O'Farrell,* 853 F.2d., 894, 902-903 (Fed. Cir. 1988).

The Patent Office contends that one of ordinary skill in the art would have had a reasonable expectation of success of protecting the *Lactobacillus johnsonii* La1 disclosed in *Carrie* due to the alleged "universality of the heat shock response in bacteria". See Office Action, page 4. Applicants respectfully submit that, not only do each of the references not disclose *Lactobacillus johnsonii* La1, but also each of the references disclose different levels of stress required to induce a response from the different strains of bacteria disclosed by the references. This variation in possible applicable stress temperatures and salt concentrations combined with the unpredictable response to the stress of the different species of bacteria disclosed in *Broadbent*, *Völker*, and *Kilstrup*, as discussed below, would not provide the skilled person with any expectation of success to arrive at the method of protecting *Lactobacillus johnsonii* La1 as in the claimed invention.

Instead, *Broadbent*, instead, pertains to heat shock responses in dairy lactobacilli. It is reported that, in specific lactobacilli, heat shock improved the ability of log phase cells to withstand an incubation at a higher temperature. To this end, *Broadbent* describes a role of heat shock proteins in heat shock-induced thermotolerance in three different species of Lactobacillus including *L. acidophilus, L. helveticus* and *L. casei*. *Broadbent* subjected each species of

bacteria to different temperatures for growth. See Table 1. For example, *L. acidophilus, L. helveticus* and *L. casei* were grown at 37°C, 37°C and 30°C, respectively. (*Broadbent*, page 13, left column, second paragraph). *Broadbent* subjected each species of bacteria to different temperatures for heat shock. For example, *L. acidophilus, L. helveticus* and *L. casei* were stressed at 50°C, 52°C and 42°C, respectively. (*Broadbent*, page 13, left column, fifth paragraph). *Broadbent* subjected each species of bacteria to different lethal challenge temperatures. For example, *L. acidophilus, L. helveticus* and *L. casei* were challenged at 63°C, 63°C and 54°C, respectively. (*Broadbent*, page 13, left column, fourth paragraph). Accordingly, the applied temperatures vary between 5°C and 10°C with respect to each strain and the resulting improved response covers the whole spectrum of the applied temperatures indicating that each strain responds individually and that the response is not predictable among the species of the Lactobacillus genus. Moreover, *Broadbent* further concludes that the magnitude of the response to heat shock varies among the different species of lactobacilli and that the effective heat treatment leads to different improvements. *Broadbent*, page 18, left column, second full paragraph. Therefore, the skilled person consulting *Broadbent* would not have been taught how to arrive at the specific method of protecting *L. johnsonii* La1 as recited in the claimed invention even if properly combinable with the other references.

Kilstrup, like *Carrie* and *Broadbent*, fail to teach or suggest protecting *Lactobacillus johnsonii* (La1). *Kilstrup*, instead, describes induction of heat shock proteins in gram-positive *Lactococcus lactis* in response to heat and salt stresses. In particular, it is reported that heat shock proteins DnaK, GroEL and GroES among 14 others are induced upon stress induction. The authors further report that, unlike in other organisms, all proteins induced via salt-stress were also seen in response to heat. Again, different temperatures are used to stress the *L. lactis*. For example, *L. lactis* was grown at 30°C and heat stress at 43°C (*Kilstrup*, page 1828, left column, second full paragraph). Moreover, different salt concentrations are used to stress the different species of bacteria. For example, *L. lactis* was exposed to 2.5% NaCl (*Kilstrup*, page 1828, left column, second full paragraph) while *B. subtilis* is exposed to 4% NaCl (*Kilstrup*, page 1836, left column, third full paragraph). In addition, *Kilstrup* describes different responses to heat and salt stress in gram-negative and gram-positive bacteria at, for example, *Kilstrup*, page 1836, left column, fourth full paragraph and right column, first full paragraph.

Furthermore, *Kilstrup* admits that conditions that incude a temperature shift of up to 43°C and addition of 2.5% NaCl stopped growth 3 to 4 hours after onset of stress. Therefore, "neither of the stress conditions are mild enough to allow for continued exponential growth" as acknowledged in *Kilstrup*. Yet, salt concentrations of up to 4% NaCl were tested in *Kilstrup* leading one of skill in the art to assume that this exposure of bacteria to even stronger stresses than the 2.5% NaCl would damage the cells in a shorter time period. *Kilstrup*, p. 1828, left column, second paragraph. Accordingly, the disclosure in *Kilstrup* is limited to teaching the skilled person the conditions necessary to achieve reliable protein expression at the expense of protecting the *L. lactis*.

Additionally, Fig. 5 on page 1834 of *Kilstrup*, illustrates inducing stress protein expression in the presence of heat (43°C) and salt (2.5% NaCl) over a time period of about 40 minutes demonstrating a time pattern of heat shock protein expression induced by the two specific conditions. This information from Fig. 5 taken together with the discussion above would have discouraged the skilled person to undertake further experiments. Therefore, *Kilstrup* is deficient in teaching or suggesting a method of protecting *L. lactis*, let alone *Lactobacillus johnsonii* La1 even if properly combinable with the other references.

Völker, like *Carrie*, *Broadbent* and *Kilstrup* fails to teach or suggest protecting *Lactobacillus johnsonii* (La1). *Völker*, instead, relates to the induction of the synthesis of stress proteins upon salt or heat stress in *Bacillus subtilis*. It is further reported that mild heat treatment showed a protective response enabling the bacteria to survive otherwise lethal temperatures. This treatment resulted in cross-protection against lethal salt stress, while salt stress was less effective in the induction of heat resistance. Specifically, *Völker* discloses exposing *Bacillus subtilis* to heat stress of 48°C to induce survival at an otherwise lethal temperature of 52°C. *Völker* also discloses exposing *Bacillus subtilis* to salt stress of 4% NaCl to induce survival of at an otherwise lethal salt concentration of 6% NaCl. However, *Völker* admits that, while salt stress may be a good inducer of general stress proteins in *B. subtilis*, it is not a good inducer of general stress proteins in *E. coli*. *Völker*, page 2125, right column, second full paragraph to page 2128, left column, first paragraph. Therefore, *Bacillus subtilis* demonstrates responses different from bacteria disclosed in the other references and from *E. coli*.

Additionally, when compared to *Kilstrup*, *B. subtilis* appears to be more flexible against stresses than the microorganism *Lactococcus lactis* of *Kilstrup*, even though *Lactococcus lactis* was tested to up to 4% NaCl, but appears to reliably express protein (heat shock protein) only up to 2.5% NaCl. As known and as can be concluded from *Völker*, *Bacillus subtilis* is an example of a robust bacterium capable of enduring massive environmental stresses and would therefore not be considered as a model organism for the more sensitive lactobacilli. Therefore, again, the results appear to be unpredictable from one organism to another.

Therefore, none of the cited documents describe a method of protecting *Lactobacillus johnsonii* La1 against stress, and each strain described in the references responds individually to stress conditions making the varied responses among the species of microorganisms unpredictable. Accordingly, Applicants respectfully submit that one of ordinary skill in the art would not have had a reasonable expectation of success of protecting *Lactobacillus johnsonii* La1 by combining *Broadbent*, *Völker*, and *Kilstrup* with *Carrie*.

Moreover, even if it would have been obvious to try to devise a method for protecting *Lactobacillus johnsonii* La1 against stress using the techniques taught in *Broadbent*, *Völker*, and *Kilstrup*, the Federal Circuit has held that "obvious to try" is not the standard under 35 U.S.C. §103. *Ex* parte *Goldgaber,* 41 U.S.P.Q.2d 1172, 1177 (Fed. Cir. 1996). "An obvious-to-try situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claim result would be obtained if certain directions were pursued." *In re Eli Lilly and Co.*, 14 U.S.P.Q.2d 1741, 1742 (Fed. Cir. 1990). Therefore, even if the cited references of *Broadbent*, *Völker*, and *Kilstrup* would have "piqued the scientist's curiosity", the disclosed conditions and responses among the bacteria studied in these references, as discussed above, are too varied and unpredictable to teach or suggest how to protect *Lactobacillus johnsonii* La1 against stress even if properly combinable with *Carrie*.

Based on at least these reasons, Applicants believe that the cited art, even if properly combinable, is distinguishable from the claimed invention and, thus, fails to render obvious the claimed invention. Accordingly, Applicants respectfully request that the obviousness rejection be withdrawn.

For the foregoing reasons, Applicants respectfully submit that the present application is in condition for allowance and earnestly solicit reconsideration of same.

Respectfully submitted,

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